REMARKS

Status of Claims

Claims 1-51 are currently pending in this application. Claims 1-22 and 39-51 are withdrawn. Claims 23-35 are rejected and claims 36-38 are objected to.

Claim Amendments

Claims 23 and 31 have been amended to recite in step (a) a cell expressing "a human α7 nicotinic acetylcholine receptor (nAChR) polypeptide having an amino acid substitution at a position corresponding to position 274 of SEQ ID NO: 2." Applicants thank the Examiner for his suggesting this language. Support for this amendment can be found, for example, on page 11, lines 21-23. For consistency purposes, in claim 23, the word "variant" was deleted in step (c) (i). For the same reasons, dependent claims 30 and 35 have been amended to replace "valine-274" with "valine". Claims 24, 28, 29 have been amended to delete the word "host" since claim 23 recites "cell." Claim 36 has been amended to remove the references to claim 1 to overcome the multiple dependency objection.

Specification Amendments

Specification has been amended to insert the Sequence ID numbers as suggested by the Examiner.

Objection to Claims 36-38

The Examiner objects to claims 36 to 38 as being in improper form since claim 36 depends from claim 1 and claim 31, and claims 37 and 38 depend from claim 36. Applicants have amended claim 36 to remove its dependency from claim 1.

Accordingly, the objection is rendered now moot and should be withdrawn.

Rejection of Claims 23-35 Under 35 U.S.C. §112, Second Paragraph

The Examiner rejects claims 23-35 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. According to the Examiner, "claims 23 to 35 are vague and indefinite because the metes and bounds of the limitation 'a variant human α7 nicotinic acetylcholine receptor (nAChR) polypeptide' are undeterminable." (See, Office Action mailed 05/15/2006, page 3). Also, the Examiner deems the claims vague and indefinite for not having an antecedent basis for "the wild-type human α7 subunit polypeptide." According to the Examiner, "all of the natural variations in the amino acid sequence of a common protein within a species of organisms are 'wild-type.'" Applicants respectfully disagree and traverse this rejection as follows.

Applicants have amended the claims to delete the word "variant" and to recite that a human α7 nAChR polypeptide has an amino acid substitution at a position corresponding to position 274 of SEQ ID NO: 2. These amendments were made in accordance with the Examiner's suggestion on page 4 of the instant Office Action. These amendments cure any and all alleged indefiniteness and make clear the metes and bounds of the invention. Specifically, the claims as amended recite, in part, providing a cell expressing a human nAChR polypeptide having an amino acid substitution at a position corresponding to position 274 of SEQ ID NO: 2. Thus, a person having an ordinary skill in the art (hereinafter, "a skilled artisan") would immediately recognize whether a referenced polypeptide is covered by the claims. Furthermore, the claims as amended do not contain references to wild type variants. Finally, Applicants have corrected a typographical error by removing the word "host" in claim 24.

Accordingly, Applicants submit that this rejection is now moot and should be withdrawn.

Rejection of Claims 23-25, 27, 29, and 30 Under 35 U.S.C. §102 (b)

The Examiner rejects claims 23-25, 27, 29, and 30 under 35 U.S.C. §102 (b) as being anticipated by the Galzi et al. (hereinafter, "Galzi et al."). According to the Examiner, the broad definition of the limitation "variant human α7 nicotinic acetylcholine receptor (nAChR) polypeptide" encompasses unlimited amino acid insertions, deletions and substitutions relative to the amino acid sequence of a "wild-type" human α7 nAChR polypeptide and thus encompasses the assay described in Figure 4 on page 503 of Galzi et al. (See, Office Action, page 4). Applicants respectfully traverse the rejection as follows.

The instant claims, as amended, recite a cell expressing a human α7 nAChR polypeptide having an amino acid substitution at a position corresponding to position 274 of SEQ ID NO: 2. In contrast, as admitted by the Examiner on page 4 of the Office Action, the assay described in Figure 4 of Galzi et al. employed a modified subunit of a chicken α7 nAChR polypeptide. The limitation that the polypeptide is "human" is in itself sufficient to distinguish claims from the assay employing a chicken polypeptide, as the assay employs a different polypeptide, namely, a chicken polypeptide instead of a human polypeptide. Moreover, the recited human nAChR polypeptide and its counterpart chicken nAChR polypeptide exhibit different pharmacological and electrophysilogical characteristics. (See, the specification, page 3, lines 7-9). Accordingly, because Galzi et al. does not disclose each and every element of the claimed invention, claims 23-25, 27, 29 and 30 are not anticipated. Therefore, this rejection is now moot and should be withdrawn.

Rejection of Claims 23, 24, 27, 29-32, 34, and 35 Under 35 U.S.C. §103(a)

Rejection over Galzi et al in view of Peng et al

Claims 23, 24, 27, 29-32, 34 and 35 are rejected under 35 U.S.C. §103(a) as being unpatentable over Galzi et al. in view of the Peng et al. (hereinafter , "Peng et al."). As discussed previously herein, the Examiner admits that the assay disclosed in Galzi et al. employs a polypeptide of chicken origin, rather than human origin. (See, Office Action, page 6). The Examiner states that the single V251T mutation described in Galzi et al. increases receptor sensitivity and reduces desensitization. The Examiner further states that the only difference between the claimed invention and the Peng et al. assay is that the Peng et al. assay employed the human α7 nAChR polypeptide which did not contain a valine to threonine substitution at the position corresponding to position 274 of SEQ ID NO: 2 of the instant application. The Examiner concludes that a skilled artisan would have found it *prima facie* obvious to have applied the structure/function analysis described in Galzi et al. to the human nAChR polypeptide described in Figure 3 of Peng et al. The Examiner states that one would have expected such substitution to yield specific information regarding the human protein because

> "the abstract of Peng et al. disclosed that the human and chicken α7 nicotinic acetylcholine receptor polypeptides demonstrated "a large species-specific pharmacological difference, despite small differences in α7 sequences." (See, Office Action, page 7).

The Examiner also states that the abstract and Fig. 4 of Peng et al. showed that the α7 nAChRs described therein were known to bind α-bungarotoxin and, therefore, a skilled artisan would have found it *prima facie* obvious to have employed α-bungarotoxin to identify compounds that antagonize the action of toxins on that receptor. According to the Examiner, the skilled artisan would have been motivated to employ a human nAChR comprising a

valine to threonine substitution like that described as V251T in Galzi et al. "because such a mutant would have been reasonably expected to have increased sensitivity and a decreased rate of desensitization relative to the unmodified receptor since the amino acid sequences from this region of the human and chicken α7 nicotinic acetylcholine receptor subunits were known to be identical." (See, Office Action, page 7). Applicants respectfully traverse the rejection.

According to the *Manuel of Patent Examining Procedure (*Eighth Edition, Latest Revision, August 2006) (hereinafter "MPEP"), three basic criteria must be met to establish a *prima facie* case of obviousness:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. (See, *MPEP* §2142).

Applicants maintain that there was no suggestion or motivation to combine Peng et al. and Galzi et al. references. As admitted by the Examiner, the human α7 nAChR polypeptide disclosed in Figure 4 on page 549 of Peng et al. does not contain a valine to threonine substitution at the position corresponding to position 274 of SEQ ID NO: 2 of the instant application. Peng et al. conducted their experiments in order to clone the α7 subunit from the SH-SY5Y cell line and to determine pharmacological properties of native receptors and functional α7 homomers expressed in *Xenopus oocytes* (*See*, Peng et al., the title and the abstract). In contrast, Galzi et al. demonstrated that the mutation of a single hydrophobic residue within the MII segment of α7 subunit of chick nAChR

corresponding to position 274 of SEQ ID NO: 2 of the instant application results in a noticeable modification of the response to acetylcholine (ACh). (See, Galzi et al., first paragraph, page 500). Therefore, the two references were directed to two different purposes: Peng et al. was directed to cloning and analyzing α7 subunit in a human cell line while Galzi et al. was directed to analyzing the specific mutation in a chick α7 subunit.

The Federal Circuit stated that "[i]n finding obviousness, the relevant question is whether a person of ordinary skill in the art, possessed with the understandings and knowledge reflected in the prior art, and motivated by the general problem facing the inventor, would have been led to make the combination recited in the claims." *In re Kahn*, 441 F.3d 977, at 988 (Fed. Cir. 2006) (internal quotations omitted). The showing of a motivation to combine must be clear and particular, and it must be supported by actual evidence. *Teleflex Inc. v. Ficosa North America Corp.*, 63 U.S.P.Q.2d 1374, 1387 (Fed. Cir. 2002).

Here, the general problem facing the inventors was to analyze a variant human α7 nAChR where valine at position 274 of SEQ ID NO: 2 had been changed. To this end, the invention provided the subunit itself, a DNA molecule encoding the subunit, methods and reagents for cloning and detecting the subunit, methods for expressing the subunit, methods of identifying compounds that modulate the subunit, methods for identifying cytoprotective compounds, and other embodiments. A skilled artisan faced with the same problem would not have been motivated to combine Peng et al. and Galzi et al. because the skilled artisan would not have thought that the information obtained from Galzi et al.'s assay could be applied to human subjects as there are important differences between chick α7 nAChR and mammalian α7 nAChR. For example, 1,1-dimethyl-4-phenylpiperazinium (hereinafter "DMPP") is a very weak partial

agonist in the chick α7 nAChR but is a highly efficacious agonist in the human α7 nAChR. (See, Specification, page 2, lines 26-30).

To summarize, nowhere in the prior art is there a suggestion or motivation to make the same amino acid substitution as in the Galzi et al.'s mutant chick α7 nAChR in human α7 nAChR.

With regard to claims 31-38, neither Galzi et al. nor Peng et al. disclose or suggest a method for identifying cytoprotective compounds comprising the steps disclosed in the claims. For this reason alone, the references do not render the claims obvious. While Peng et al. demonstrated that α7 nAChR binds α-bungarotoxin, nowhere does Peng et al. disclose or suggest a method of identifying cytoprotective compounds. The reference is directed to determining the pharmacological properties of native receptors and functional human α7 homomers expressed in *Xenopus oocytes*. To the extent the effect of α-bungarotoxin was studied, the purpose of this experiment was to compare the pharmacological properties of human and chick native and mutant α7 nAChRs, and not to identify any cytoprotective compounds. There is no discussion at all regarding a possible use of disclosed α7 nAChR to identify cytoprotective compounds. Accordingly, the method for identifying cytoprotective compounds is not rendered obvious by Peng et al. in view of Galzi et al.

Moreover, Applicants provided evidence of unexpected results. According to the Federal Circuit, unexpected results provide objective evidence of non-obviousness. *Specialty Composites v. Cabot Corp.*, 845 F.2d 981 (Fed. Cir. 1988). Even if a skilled artisan were motivated to combine Galzi et al. and Peng et al. (for which Applicants submit there is no motivation, suggestion or teaching to do so), the skilled artisan would have expected that the substitution of the identical amino acid in human α7 nAChR would have resulted in similar pharmacological and electrophysiological changes as were observed in mutant

chick α7 nAChR. However, while there are some similarities between mutant human α7 nAChR and the analogous chick α7 nAChR, the receptors differ in their reaction to dihydro-β-erythroidine hydrobromide (hereinafter "DHβE") and d-turbocurarine chloride (hereinafter "d-TC"). DHβE activated the mutant human α7 nAChR inward current only weakly, compared to a 66% agonist-like effect at chick α7 nAChR, while d-TC did not activate inward currents at the human α7 nAChR compared to the full response at chick α7 nAChR. (See, Specification, page 32, lines 17-22). In another important difference, while mutant human α7 nAChR showed inward rectification of the ACh response (there was little current response at cell potentials above 0 mV compared to the current response at negative cell potentials), the analogous mutant chick α7 nAChR did not show such rectification. (See, Specification, the paragraph bridging pages 32 and 33).

Accordingly, the references do not render the invention obvious as 1) a skilled artisan would not have been motivated to combine the cited references and 2) Applicants have demonstrated unexpected results.

Rejection over Galzi et al in view of Peng et al in view of Elliot et al

The Examiner further rejects claims 23, 24, 27, 29-32, 34, and 35 under 35 U.S.C. §103(a) as being unpatentable over Galzi et al. and Peng et al. in view of Elliott et al. (U.S. Patent No. 5,910,582) (hereinafter, "Elliott et al."). The Examiner states that Elliott et al. describe the incorporation of recombinant polynucleotides encoding mammalian neuronal nicotinic acetylcholine receptors, and expressly including the human α7 nicotinic acetylcholine receptor of Peng et al., into mammalian host cells for the purpose of identifying agonists and antagonists thereto. The Examiner maintains that it would have been obvious to a skilled artisan to have employed a human α7 nAChR comprising a valine to threonine substitution in such a host cell and assay. Applicants respectfully traverse the rejection.

As admitted by the Examiner, the human nAChR disclosed in Elliott et al. is different than the mutant human nAChR comprising a substitution at a position corresponding to position 274 of SEQ ID NO: 2. The human nAChR disclosed in Elliott et al. correspond to the receptor disclosed in Peng et al. As Applicants explained previously herein, the receptor disclosed in Peng et al. is different from the receptor cloned by Applicants, and there was no teaching, suggestion, or motivation to combine Galzi et al. with Peng et al. Since Elliott et al. disclose the same receptor, except expressed in mammalian host cells, the same arguments equally apply to this rejection. In brief, there are important differences between chick and human nAChRs; neither of the references contain motivation to combine, whether expressed or in the nature of the problem to be solved; neither of the references disclose or suggest a method to identify cytoprotective compounds; and Applicants have demonstrated unexpected results.

Accordingly, the references do not render the invention obvious. In view of the above arguments, Applicants respectfully submit that the rejections of claims 23, 24, 27, 29-32, 34, and 35 under the 35 U.S.C. § 103 are improper and should be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. Sections 102, 103, and 112. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Should the Examiner have any questions concerning the above, she is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

If any additional fees are incurred as a result of the filing of this paper, authorization is given to charge Deposit Account No. 23-0785.

Respectfully submitted,
Clark A. Briggs *et al.*

Wood, Phillips, Katz, Clark & Mortimer
500 West Madison Street
Suite 3800
Chicago, IL 60662-2511

Tel.: (312) 876-2109
Fax.: (312) 876-2020

Lisa V. Mueller
Registration No. 38,978
Attorney for Applicants